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ASSESSMENT OF *CLOSTRIDIOIDES DIFFICILE* INFECTION RISK AND OUTCOMES AMONG PATIENTS DIAGNOSED WITH CANCER: A RETROSPECTIVE COHORT STUDY OF THE UNITED STATES VETERANS HEALTHCARE SYSTEM

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by

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Dedication

I dedicate this dissertation to my mother and grandparents, who worked tirelessly to ensure a bright future for my sister and me. I also dedicate this dissertation to Kathryn, Emilia, John and Nolan, who have irrevocably put me on track for a happy and fulfilling life.

Acknowledgements

I would like to acknowledge my supervisors, Professor Jim Koeller and Dr. Kelly Reveles, for their patience and support. Professor Koeller provided my initial inspiration to pursue research interests, and granted me the freedom and flexibility to find my own way. Dr. Reveles' tremendous work ethic and intellectual curiosity drive me to be a better academician. Without her, I certainly would not be where I am today. I would also like to acknowledge and thank my dissertation committee members, Drs. Grace Lee and Eugene Kreys. I sincerely appreciate your guidance and mentorship during my time as a student.

ASSESSMENT OF *CLOSTRIDIOIDES DIFFICILE* INFECTION RISK AND OUTCOMES AMONG PATIENTS DIAGNOSED WITH CANCER: A RETROSPECTIVE COHORT STUDY OF THE UNITED STATES VETERANS HEALTHCARE SYSTEM

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The University of Texas at Austin, 2019

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Clostridioides difficile infection (CDI) is an urgent public health problem in the United States (U.S.). Nearly half a million patients suffer from and 29,000 patients die from CDI annually in the U.S. Importantly, prior studies have noted a disproportionate incidence of CDI among cancer patients. This may be due to a number of factors, including the underlying disease, immunosuppression, healthcare exposures, or medication exposures. Despite these trends, few studies have assessed cancer as an independent risk factor for CDI. Furthermore, limited data exist to describe the effect cancer has on CDI health outcomes or the most appropriate treatment approaches for cancer patients who develop CDI. The objectives of this study were to: 1) define the risk of CDI among cancer patients compared to non-cancer patients, 2) compare CDI clinical outcomes of patients with and without cancer, and 3) compare the effectiveness of CDI

antibiotic therapy on CDI clinical outcomes among cancer patients. This was a retrospective cohort study of CDI and non-CDI patients in the U.S. Veterans Health Administration. Data were obtained from the Veterans Affairs Informatics and Computing Infrastructure. A series of multivariable logistic regression models were conducted to determine the impact of cancer on CDI risk and health outcomes, including demographics, comorbidities, and healthcare and medication exposures as covariates. In aim 1, cancer (overall) was an independent risk factor for CDI (OR 1.41; 95% CI 1.35-1.47). Metastatic disease was the strongest cancer predictor of CDI (OR 4.68; 95% CDI 4.02-5.45). In aim 2, cancer was associated with an increased risk for 30-day mortality following the CDI episode (OR 1.44; 95% CI 1.33-1.55). In aim 3, there was no statistically significant difference in 30-day mortality among CDI cancer patients who received metronidazole or oral vancomycin (OR 1.08; 95% CI 0.87-1.34). These data will be important for informing further local and public health initiatives for preventing CDI in high-risk groups, like cancer patients, and guiding treatment approaches.

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CHAPTER 1

AN OVERVIEW OF *CLOSTRIDIOIDES DIFFICILE* INFECTION

MICROBIOLOGY AND PATHOGENESIS

Clostridioides difficile is a Gram-positive, spore-forming, anaerobic bacterium. It is ubiquitous in the environment, with *C. difficile* spores found in soil, food, and healthcare facilities. It can also be part of the gastrointestinal microbiome of humans. Colonization rates vary by age and by healthcare exposures. The majority (up to 90%) of healthy newborns are colonized with *C. difficile*, while very few (<2%) healthy adults are colonized. In contrast, adults who are hospitalized or in long-term care facilities can have much higher colonization rates (up to 50%).[1]

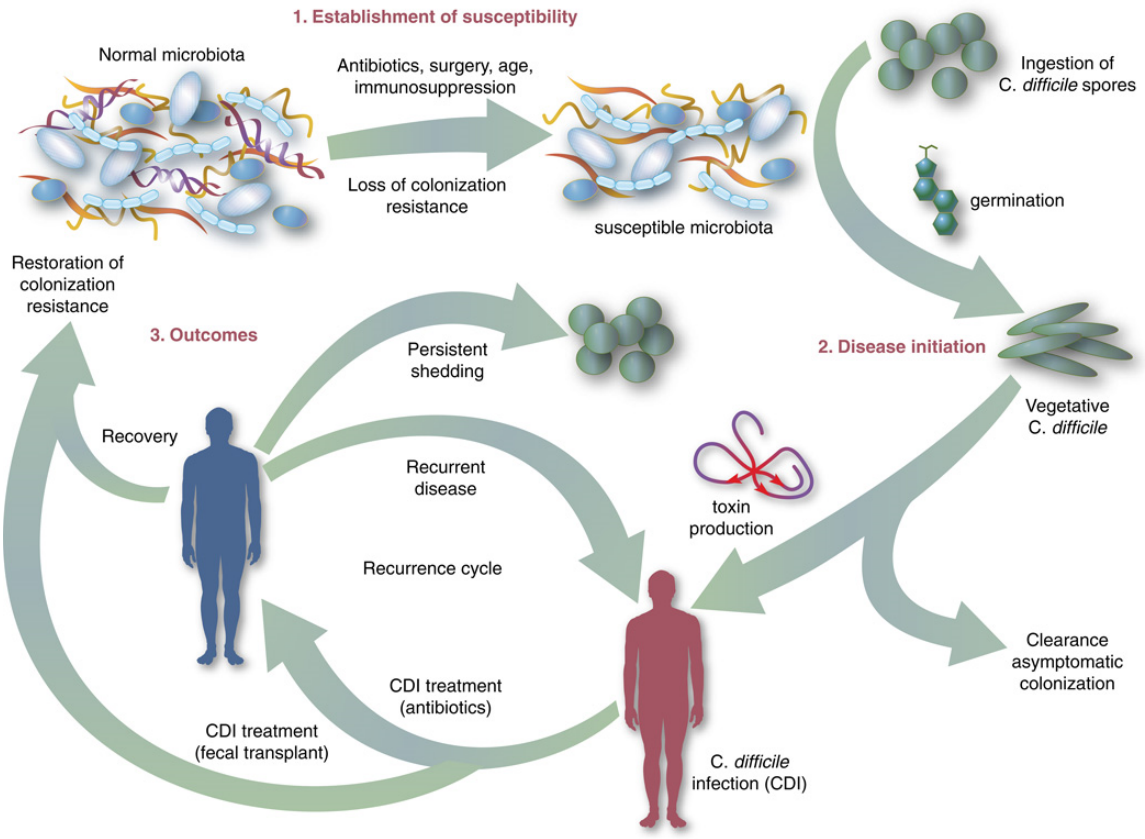
Table 1.1 Gut colonization rates of *C. difficile* by age and healthcare exposures[1]

Population	% colonized
Healthy neonates & infants	18-90%
Healthy adults	0-15%
Elderly, long-term care residents	0-51%
Hospitalized patients	
General inpatients	4-29%
Elderly	1-15%
Cystic fibrosis	18-47%
Healthcare personnel	0-13%

Transmission can occur between hosts via the fecal-oral route as the vegetative form of *C. difficile* or as spores.[2] In healthy patients, the gut ecosystem contains trillions of bacterial cells that play a critical role in human health. The composition and diversity

of the gut microbiota interact with the human host to prevent infection, limit accumulation of toxins, aid in digestion and metabolism, and provide for energy and nutrient extraction.[3] Disruption of the normal gut microbiota is the mechanism by which *C. difficile* infection (CDI) develops in those patients who are already colonized with *C. difficile* or those who acquire *C. difficile* spores during a time of gastrointestinal microbiome dysbiosis. An overview of CDI pathogenesis in outlined in Figure 1.1.

Figure 1.1 Pathogenesis of CDI[4]



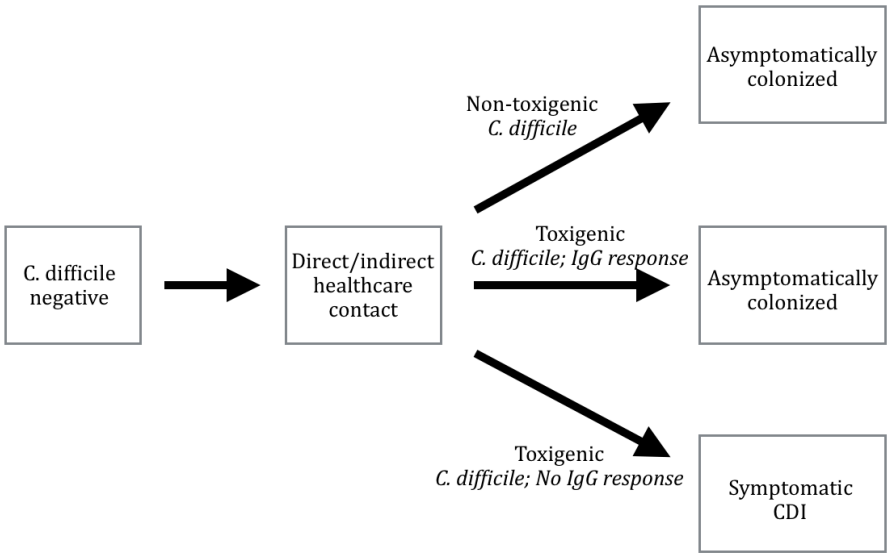
Once colonization is established, development of disease occurs due to sporulation and toxin production. Spores can germinate and produce new vegetative cells when conditions become favorable. Substances present in the intestine, most notably bile acids, amino acids, and short chain fatty acids (SCFAs) play a role in the regulation of *C. difficile* in the gut. For example, bile acids can induce spore germination into actively replicating vegetative cells. The primary bile acid taurocholate promotes germination,[5] while the secondary bile acid deoxycholate acts as a competitive inhibitor of taurocholate and suppressant of vegetative growth.[6] The production of secondary bile acids by commensal microbiota modulates susceptibility to CDI. Loss of secondary bile acids in the colon following antibiotic treatment is strongly associated with susceptibility to CDI, and recovery from recurrent CDI following fecal microbiota transplantation (FMT) is highly correlated with recovery of secondary bile acid levels.[7]

Toxins A and B (TcdA and TcdB, respectively) are the two main *C. difficile* virulence factors. It is currently unknown whether cellular adhesion or biofilm production is involved in this process. After uptake into the cell, TcdA causes cytoskeletal alterations that lead to the disruption of tight junctions between epithelial cells and allow both toxins to cross the epithelial barrier. Various immunomodulatory mediators, such as IL-6 and IL-8 by intestinal epithelial cells, are activated in response to the toxins, and further inflammation occurs around the epithelial cells.[2,8] It is the inflammatory response and damage to the gastrointestinal lining that prompt symptomatic infection.

Certain strains of *C. difficile* are non-toxin-producing; thus, colonization does not lead to clinical disease. Furthermore, patients with adequate IgG immune response to

toxin production may also be asymptomatically colonized. It is patients who cannot mount an immune response to toxins who develop symptomatic CDI (Figure 1.2).

Figure 1.2 Model for clinical response after *C. difficile* colonization



Given that CDI is a bacterial infection, it is treated with antibiotic therapy as described later. This therapy can further disrupt the gastrointestinal microbiome, leading to inadequate recovery of microbial diversity and function. If CDI is not adequately treated or spores remain after antibiotic therapy, the process of germination, vegetative growth, and toxin production can begin again, leading to recurrent disease. It is estimated that 20-25% of patients who experience an initial CDI episode will have a recurrence.[9]

CLINICAL PRESENTATION AND DIAGNOSIS

Diarrhea is the most common manifestation of CDI. In most patients, diarrhea is mild to moderate (3-10 loose, watery stools in 24 hours) and may be self-limiting following discontinuation of inciting antibiotic therapy. Leukocytosis, fever, hematochezia, nausea, anorexia, and cramping may also occur.[2] In more severe forms of the infection, pseudomembranes, which are elevated yellow plaques, develop on the intestinal epithelium and may be seen upon endoscopy. [2] In the most severe cases, CDI may present as fulminant colitis. Patients may present with severe lower quadrant or abdominal pain, and diarrhea can be absent in the case of paralytic ileus. Toxic megacolon, which is an acute toxic colitis with dilatation of the colon, may also occur with severe systemic symptoms.[2]

The diagnosis of CDI is based primarily on clinical presentation, but imaging studies may also aid in diagnosis.[10] The 2017 Society for Healthcare Epidemiology and Infectious Diseases Society of America (SHEA/IDSA)[10] Clinical Practice Guidelines for CDI recommend clinical suspicion of CDI if the patient has frequent, new-onset diarrhea (≥ 3 unformed stools per day). Fever (> 102°F), abdominal distention, and leukocytosis may also be present. CDI should also be suspected in those patients presenting with CDI risk factors as described later.

The gold standard for CDI diagnosis is the stool test. Tests should assess for the presence of toxigenic *C. difficile*, which may necessitate a combination of different assays. An overview of currently available diagnostic tests is provided in Table 1.2.

Table 1.2 An overview of available CDI stool tests[11]

Test	Detects	Sensitivity	Specificity
Toxigenic culture	*C. diff* cells or spores	High	Low
Nucleic acid amplification test	Toxin genes	High	Moderate
Glutamate dehydrogenase	*C. diff* antigen	High	Low
Cytotoxicity assay	Free toxins	High	High
Toxin enzyme immunoassay	Free toxins	Low	Moderate

RISK FACTORS

Antimicrobial therapy is considered the most important risk factor for CDI. This is due to the disruption of the normal gut microbiota, which can occur in as little as one dose for surgical prophylaxis.[12] Longer duration of therapy and exposure to multiple agents increases the risk of CDI development.[13] CDI risk is more common with antibiotics that extensively disrupt the gastrointestinal microbiota, such as clindamycin, carbapenems, and extended-spectrum penicillins and cephalosporins (Table 1.3).

Table 1.3 Antibiotics commonly associated with CDI risk[14]

Commonly associated	Occasionally associated	Rarely associated
Clindamycin	Penicillins	Aminoglycosides
Carbapenems	Cephalosporins (1^{st}/2^{nd} gen.)	Daptomycin
Cephalosporins (3^{rd}/4^{th} gen.)	Trimethoprim-sulfamethoxazole	Tetracyclines
Fluoroquinolones	Macrolides	Vancomycin

The risk of CDI can vary geographically, though, depending on the resistance profiles of strains compared to the respective antimicrobial agent employed.[15] Resistance to antibiotics used to treat CDI has not posed a significant threat.[8]

Other non-antibiotic classes of medications have been associated with CDI as well. First, gastric acid suppressants increase gastrointestinal pH. The pH in the stomach and duodenum promotes changes in the gut microbiota, inhibiting the growth of some species like *Bifidobacterium*;[16] thus, gastric acid suppressants can decrease microbial diversity and predispose patients to CDI. Secondly, proton pump inhibitors (PPIs) can target bacterial proton pumps, potentially interfering with microbial function in the gut. A recent meta-analysis of 42 studies (n=313,000) found that PPI use increased the risk for initial (OR 1.74, 95% CI 1.47 to 2.05; 39 studies) and recurrent (OR 2.51, 95% CI 1.16 to 5.44; three studies) CDI compared to non-use.[17] A second class of non-antibiotics that may increase the risk for CDI includes specific chemotherapeutic agents.[18] A more thorough discussion of the association between cancer, chemotherapy, and CDI will be discussed in Chapter 2.

Other CDI risk factors are primarily related to poor underlying immune response and healthcare exposures. Inadequate immune response as a function of older age, severe underlying disease, or immunosuppression can predispose to CDI due to insufficient IgG response to *C. difficile* toxins. Exposure to *C. difficile* spores through environmental exposures is another important risk factor. Specifically, hospitalization, inadequate isolation from other infected patients, and long-term care residence have been associated with CDI. The risk of CDI increases for each additional day a patient is hospitalized.[15]

TREATMENT

The 2017 SHEA/IDSA[10] Clinical Practice Guidelines for CDI guide infection diagnosis and management in adult and pediatric patients. Guidelines currently recommend that clinicians discontinue therapy with inciting antimicrobial agents, which may affect the risk of recurrence. The clinician should then evaluate the patient's age, white blood cell (WBC) count, 24-hour bowel movement count, and peak serum creatinine (SCr) level, which help indicate the severity of CDI. It is imperative, then, to initiate empiric antibiotic therapy, particularly in situations with a laboratory delay.

In accordance with the above guidelines, oral vancomycin or fidaxomicin are strongly recommended to treat the first episode of CDI (non-severe and severe). Oral metronidazole is weakly recommended in non-severe CDI if oral vancomycin or fidaxomicin are unavailable (Table 1.4). Regardless of severity, treatment is recommended for ten days. An initial episode of fulminant CDI (CDI with shock, ileus, or megacolon) may be treated with oral vancomycin in combination with intravenous metronidazole. If oral metronidazole is used for the initial episode of CDI, oral vancomycin may be used to treat the first recurrence. Otherwise, a prolonged and tapered oral vancomycin regimen or fidaxomicin are recommended for first recurrence CDI. Subsequent recurrences may be treated with tapered and pulsed oral vancomycin (Vancomycin 125 mg PO 4 times daily for 10-14 days, then 2 times daily for 7 days, then daily for 7 days, and then every 2-3 days for 2-8 weeks), oral vancomycin followed by oral rifaximin, fidaxomicin, or fecal microbiota transplantation, although the expert panel recommends reservation of the fecal transplant for patients suffering at least two recurrences.[10]

Table 1.4 Recommendations for the treatment of CDI[10]

Clinical definition	***Recommended treatment***
Initial episode, non-severe	Vancomycin 125 mg PO 4 times daily for 10 days ***or*** FDX 200 mg PO twice daily for 10 days ***or*** metronidazole 500 mg PO 3 times daily for 10 days if neither prior agent is available
Initial episode, severe	Vancomycin 125 mg PO daily for 10 days ***or*** FDX 200 mg PO twice daily for 10 days
Initial episode, fulminant	Vancomycin 500 mg PO or by nasogastric tube ***and*** metronidazole 500 mg IV 3 times daily; Vancomycin PR may be added if ileus
First recurrence	Vancomycin 125 mg 4 times daily for 10 days ***or*** tapered and pulsed vancomycin regimen* ***or*** FDX 200 mg twice daily for 10 days
Second or subsequent recurrence	Tapered and pulsed vancomycin regimen* ***or*** vancomycin 125 mg 4 times daily for 10 days, followed by rifaximin 400 mg 3 times daily for 20 days ***or*** FDX 200 mg twice daily for 10 days ***or*** fecal microbiota transplant**

FDX = fidaxomicin, PO = by mouth, PR = by rectum, IV = intravenously

*Vancomycin 125 mg PO 4 times daily for 10-14 days, then 2 times daily for 7 days, then daily for 7 days, and then every 2-3 days for 2-8 weeks

**Recommended beyond 2nd recurrence (i.e., after 3rd episode)

BURDEN OF ILLNESS

C. difficile is the most common cause of infectious diarrhea in healthcare settings, accounting for 20-30% of antibiotic-associated diarrhea cases.[15,19] In a study of U.S. hospitalized adults, Reveles et al.[20] found that CDI incidence rates increased from 4.5 to 8.2 CDI discharges per 1,000 total adult discharges between 2001 and 2010. By analyzing Healthcare Cost and Utilization Project data, Lucado et al.[21] found that the U.S. hospitals saw a 2.5-fold increase in the number of hospitalizations with any CDI discharge diagnosis between 2000 and 2008. CDI discharge rates increased most dramatically among persons aged 65 years or greater, with 5-fold the rate of discharges among those aged 45-64 years.[15,22] During the same period, reports of CDI epidemics were found to occur in Canada, with mortality increasing drastically between 1997 and 2005.[23-26] Although limited *C. difficile*-associated disease incidence data is available across Europe, laboratories in thirty-four European countries estimated a CDI incidence of 4.1 per 10,000 patient-days per hospital (range 0.0 – 36.3) in 2008.[27,28]

A particular hypervirulent *C. difficile* strain, characterized as North American pulsed-field type NAP1, as type BI by restriction enzyme analysis, and as PCR ribotype 027 (NAP1/BI/027), has been credited partially for the rise of CDI.[8] By 2008, CDI cases due to the NAP1/BI/027 strain were reported by hospitals in forty U.S. states and all Canadian provinces, becoming endemic in some North American healthcare settings.[29-31] In a survey regarding the spread of ribotype 027 in Europe, this *C. difficile* strain had been found in sixteen European countries by 2008.[32] This same year, Bauer et al.[28] estimated a 5% prevalence of ribotype 027 across thirty-four European countries. More recently, the emergence of the ribotype 078 has been associated with disease in younger patients more frequently prescribed fluoroquinolones and with community-associated or indeterminate CDI, as compared to ribotype 027 patients in the Netherlands.[33]

OUTCOMES AND COST

To inform policy decisions regarding prevention and treatment, an understanding of the health outcomes and economic impact of CDI is essential. In a retrospective analysis of discharge data, the overall in-hospital mortality rate was 7.1% for adult patients with CDI. This mortality rate increased from 6.6% in 2001 to 7.2% in 2010. Median hospital length of stay (LOS) remained stable across the study period, at approximately eight days.[20] In an analysis of age group trends, elderly patients (≥65 years) had significantly higher rates of mortality (8.8%) compared to adults (18-64 years; 3.1%) and pediatrics (<18 years; 1.4%; $p < 0.0001$). LOS was also highest in elderly patients compared to adults and pediatric (8 vs. 7 vs. 6; $p<0.0001$).[34]

Schweiser et al.[35] estimated the burden of CDI in the U.S. based on multicenter studies between 2000 and 2014. Compared to other hospitalized patients, those with CDI were found to suffer a 2.5-fold increase in mortality, based on a pooled analysis of 22 studies. This same analysis found a mean CDI-attributable cost of the index hospitalization to range from $8,426 to $48,500, although only four studies of questionable quality were used in this analysis. Mean readmission costs were found to be $14,847, while mean CDI-attributable LOS was 12.3 days.

To further evaluate the costs of CDI on the U.S. healthcare system, Zhang et al.[36] conducted a meta-analysis using studies investigating the direct medical cost associated with CDI hospital management. The average price of CDI case management was $42,316, with an average CDI-attributable cost of $21,448 in 2015 U.S. dollars. The total annual CDI-attributable cost in the U.S. was estimated at $6.3 billion (range $1.9-$7.0), with 2.4 million days of inpatient stay required each year. A significantly lower LOS and median cost after diagnosis has been reported in guideline-treated patients with mild-to-moderate CDI (5 vs. 7 days, $p=0.03$; $5257.85 vs. $7680.56, $p=0.03$).

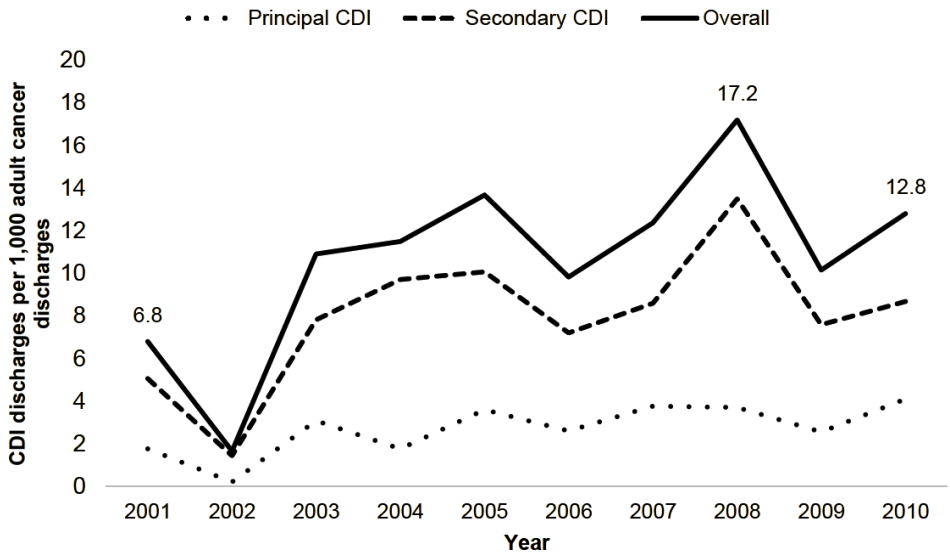
CHAPTER 2

CURRENT EPIDEMIOLOGY OF CDI IN CANCER PATIENTS

CDI INCIDENCE IN CANCER PATIENTS

The incidence of CDI among cancer patients is higher than the general population. In a study of U.S. hospitalized adults, Reveles et al. [20] found that CDI incidence increased from 4.5 to 8.2 CDI discharges per 1,000 total adult discharges between 2001 and 2010. This compares to an increase in incidence from 6.8 to 12.8 discharges per 1,000 adult cancer discharges from 2001 to 2010 (Figure 2.1).[37] A multicenter study of 11 cancer centers revealed a pooled CDI incidence rate twice that of all other U.S. patients (15.8 vs. 7.4 per 10,000 patient-days).[38]

Figure 2.1 CDI incidence among U.S. hospitalized adults with cancer, 2001-2010[37]



CDI incidence rates also vary by cancer type. In our prior work, the incidence of CDI in solid tumor cancer patients (6.8 discharges per 1,000 adult solid cancer discharges) was lower than that of hematologic cancer patients (17.3 discharges per 1,000 adult blood cancer discharges) over the study period.[37] An epidemiologic study of hematopoietic stem cell transplant (HSCT) patients at a tertiary care hospital revealed CDI rates were 9-fold higher compared to general patients, and 1.4-fold higher compared to other cancer patients. A small pilot study performed to compare *C. difficile* strains among HSCT, and general ward patients revealed a variety of strains among HSCT patients and a much more significant presence of the NAP1/BI/027 strain among non-cancer patients, suggesting the epidemiology in this population is complex. [39]

CDI RISK FACTORS AMONG CANCER PATIENTS

The significantly higher rates of CDI in cancer patients may be due to several factors. First, lengthy or recurrent hospitalizations lend themselves to greater *C. difficile* exposure, and as many as 32% of cancer patients undergoing chemotherapy experience at least one hospitalization.[40] Compared to non-oncology inpatients, oncology inpatients have also been found to have longer median LOS.[40-42] Suda et al.[43] found that compared to 26% of non-oncology patients, 36% of cancer patients experienced a LOS >7 days. In 2009, NHDS data estimated that the average LOS for an adult primary cancer diagnosis was 1.6 days longer than a non-cancer diagnosis.[44]

Immunosuppression due to host immunosenescence, the disease, or drug therapy could predispose cancer patients to clinical infection, rather than colonization, as the patient might not be able to mount as strong of a host response. Older age,[28,41] severe underlying disease,[28,41] and immunosuppressive therapy[45,46] have all previously been associated with CDI. Furthermore, prior studies have found that immunosuppressed patients who develop CDI are at higher risk for poor clinical outcomes.[47,48] In a study of 5,594 adult patients receiving cancer treatment, CDI-related mortality was 19.7%.[49] Neutropenia was found to be an independent predictor of CDI-related mortality.[49]

CDI risk by cancer type is likely also related to several factors. Patients with hematologic malignancies might receive antibiotics at a higher rate due to a higher incidence of neutropenic fever resulting from cytotoxic chemotherapy and direct effects on host immunity.[50] Furthermore, patients with blood cancers tend to have a longer length of stay during hospitalizations compared to solid tumor patients.[44] Lastly, blood cancers have the therapeutic option of HSCT. When comparing HSCT recipients versus other oncology patients, Chopra et al.[51] reported HSCT recipients to have 1.4 times higher CDI rates. It is hypothesized these differences are due to chemotherapy regimens and

antibiotic use leading up to transplantation, in addition to a prolonged hospital stay.[47,52-54] The distinction between blood cancers versus solid cancers is of importance in CDI prevention and treatment. Due to the increased risk associated with hematologic malignancies, more diligent antimicrobial stewardship may be warranted along with potentially more aggressive CDI treatment.[37]

Cancer patients are frequently exposed to medications and other factors that can alter the gut microbiota or alter the host response. The following classes of medications or therapies are used frequently among cancer patients and have been previously associated with CDI: antibiotics[28,41,45,46,55], certain chemotherapeutic agents[18], gastric acid suppressing medications[41], and manipulation of the gastrointestinal tract (e.g., enteral feedings, enemas, stimulants).[56]

Chemotherapeutic agents have been shown previously to increase the risk for CDI; however, most studies have been case reports or case series.[48] In a retrospective review of patients with gynecologic malignancies treated with paclitaxel-based chemotherapy regimens, the risk of CDI was estimated to be 2.2% in patients receiving standard-dose regimens and as high as 20% in patients receiving high-dose regimens.[57] An additional study of 33 patients with primary ovarian malignancy treated with cisplatin-based combinations examined the incidence of CDI, finding that two patients (6.1%) developed severe CDI. After successful treatment, a patient developed a CDI relapse after a subsequent dose of cisplatin, which did not occur again after switching to a carboplatin alternative.[58] In neutropenic patients with hematologic malignancies, CDI occurred in 7% of all myelosuppressive chemotherapy cycles.[59] Other reports have associated the following chemotherapeutic agents with CDI: bleomycin, carboplatin, cisplatin, cyclophosphamide, cytarabine, doxorubicin, etoposide, methotrexate, paclitaxel, topotecan, vinblastine, vinorelbine, and 5-FU.[48,52,57,58,60-69]

PATHOPHYSIOLOGIC MECHANISMS BY WHICH CANCER INCREASES CDI RISK

While antibiotic-associated CDI pathogenesis is well understood, this is not the case for chemotherapy-associated disease, as mentioned above. It has been proposed that similar to antibiotics, chemotherapeutic agents like methotrexate may lead to a disruption of gut microbiota, enabling alternative bacterial growth.[70] The chemotherapeutic drugs methotrexate and 5-FU maintain the ability to cause severe intestinal mucositis since apoptosis is induced through inhibition of DNA and RNA synthesis.[48] In rat models, methotrexate was shown to disrupt intestinal protein metabolism, increase proteolysis, and enhance cytokine response, which could promote *C. difficile* pathogenesis.[48,71] DNA topoisomerase inhibitors, such as irinotecan and topotecan, can also result in severe mucositis, but an increase in CDI has never been illustrated.[48]

Other proposed mechanisms of increased pathogenesis in the cancer population include inflammatory changes induced by chemotherapy, necrosis in the intestinal tract that promotes an anaerobic environment, and delayed reestablishment of normal gut microbiota increasing the possibility of relapse. The exact pathogenesis is unclear at this point. Confounders present due to the disease itself and concomitant treatments make research challenging.[48]

TREATMENT OF CDI IN CANCER PATIENTS

At this point, treatment of CDI in cancer patients follows the same guidelines as the general population. The SHEA-IDSA Clinical Practice Guidelines for CDI provide guidance for the diagnosis and management of CDI in adult patients.[10] Guidelines currently recommend that clinicians discontinue therapy with inciting antimicrobial agents, which may affect the risk of recurrence. Oncology specialists maintain the additional consideration of chemotherapeutic agents, which may also have an influence. The clinician then evaluates the patient's age, WBC count, and peak serum creatinine level, which help indicate the severity of CDI. Assessing severity by WBC count presents a challenge in patients who frequently suffer from neutropenia.

Following the general guidelines, metronidazole has fallen out of favor due to recent clinical trial data indicating inferior effectiveness compared to vancomycin. In a randomized controlled trial, CDI treatment success was significantly higher in patients treated with oral vancomycin (81%) compared to metronidazole (73%) ($p=0.02$).[72] Comparative efficacies of metronidazole and vancomycin have not been studied in cancer patients, but the response rate to oral metronidazole was found to be 90.9% in a cohort of neutropenic patients with hematologic malignancies.[59]

The clinical practice guidelines now recommend oral vancomycin or fidaxomicin as first-line therapy for all patients; however, recent clinical trial data support the use of fidaxomicin in cancer patients. In an analysis of Phase 3 fidaxomicin clinical trial data, clinical cure of CDI was higher (though not quite statistically significant) in patients treated with fidaxomicin compared to vancomycin (OR 2.0; $p=0.065$). Importantly, risk for recurrence was significantly lower among fidaxomicin-treated patients (OR 0.37; $p=0.018$).[73] Despite the higher drug acquisition costs, using fidaxomicin as first-line therapy for cancer patients has been shown to be cost-effective.[74]

KNOWLEDGE GAPS

As a common and increasingly burdensome healthcare-associated infection, CDI has been the target of focused epidemiological studies and infection control strategies.[15,20] Recent data has also demonstrated the increased incidence of CDI among cancer patients.[37,39] In particular, rates of CDI among patients with hematologic cancers are alarming, and limited evidence supports poorer outcomes in this population compared to the general population and overall cancer population.[20,37] It is apparent, however, that sufficient data to assess risk, predict outcomes, and provide optimal care to this population are lacking.[37,48] Although much evidence supports the biological plausibility of cancer patients suffering an increased risk of CDI, much of the reported evidence has not been corroborated by large, high-quality observational studies or clinical trials.

Knowledge of the risk of CDI among patients diagnosed with cancer represents a fundamental gap in knowledge. Although prior studies have highlighted the incidence of CDI among cancer patients, a quantifiable risk of CDI associated with disease allows cancer patients to be more readily identified as a high-risk population in whom antimicrobial stewardship and other infection control processes should be targeted. These data could also serve as justification for further work for elucidating the mechanisms behind these associations.

The limited cancer-specific treatment data precludes the use of evidence-based management strategies, particularly considering the lack of high quality data supporting the risk of CDI among patients with a cancer diagnosis or undergoing chemotherapeutic treatment. Further studies are needed to evaluate the comparative-effectiveness of CDI-targeted antibiotic therapies in this high-risk population.

In the future, clinicians may tailor CDI therapy for this population specifically. For example, clinicians might choose a more aggressive or costly therapy in cancer patients to improve clinical outcomes. Despite the importance of this knowledge, information regarding the risk of CDI among cancer patients in U.S. is currently not well described.

CHAPTER 3

SPECIFIC AIMS AND HYPOTHESES

SPECIFIC AIM 1: DEFINE THE RISK OF CDI ASSOCIATED WITH A CANCER DIAGNOSIS, COMPARED TO A GROUP OF NON-CDI CONTROLS

Hypothesis 1.1: The risk of CDI is greater in patients with a cancer diagnosis.

Hypothesis 1.2: Patients with hematologic malignancy will have a higher risk of CDI compared to non-hematologic cancers.

SPECIFIC AIM 2: COMPARE CDI CLINICAL OUTCOMES OF PATIENTS WITH AND WITHOUT CANCER

Hypothesis 2.1: CDI patients with cancer will have higher risk of 30-day mortality, 60-day CDI recurrence, and hospital LOS compared to non-cancer patients.

SPECIFIC AIM 3: COMPARE CDI CLINICAL OUTCOMES AMONG PATIENTS WHO RECEIVE METRONIDAZOLE OR VANCOMYCIN

Hypothesis 3.1: Patients who receive oral metronidazole will have higher risk for 30-day mortality, 60-day CDI recurrence, and hospital LOS compared to patients who receive oral vancomycin.

CHAPTER 4

STUDY APPROACH

STUDY DESIGN

This was a retrospective study of patients with their first occurrence of CDI receiving care at any inpatient VHA facility in the United States. Aim 1 follows a case-control design, whereas aims 2 and 3 are retrospective cohort studies. Data for this study were obtained from the VA Informatics and Computing Infrastructure (VINCI), which includes administrative, clinical, laboratory, and pharmacy data repositories that are linked using unique patient identifiers. This study was approved by the Institutional Review Boards at UT Health San Antonio and the South Texas Veterans Health Care System Research and Development Committee.

STUDY POPULATION

The CDI cohort was created by identifying patients 18-89 years old who had any inpatient or outpatient *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) code for CDI (008.45) plus a positive CDI stool test (e.g., toxin enzyme immunoassay or nucleic acid amplification test ± glutamate dehydrogenase antigen test) during the visit or within 7 days of the visit from October 1, 2002 through September 30, 2014. CDI patients were also required to have received active CDI therapy

(oral vancomycin, metronidazole, fidaxomicin) during the CDI encounter. Patients with an ICD-9-CM code for CDI (008.45) in the year prior to study inclusion were excluded. A control group was created by identifying a random sample of VHA patients without a CDI ICD-9-CM code for the duration of the study period and matching 2:1 (control to CDI) by treatment setting (inpatient or outpatient) and fiscal year of visit.

INDEPENDENT VARIABLES

Cancer diagnosis in the year prior to cohort inclusion was defined using ICD-9-CM codes and was coded overall and by cancer type (Table 4.1).

Table 4.1 Cancer diagnosis ICD-9-CM codes

Cancer type	ICD-9-CM codes
Malignant neoplasm of the lip, oral cavity, and pharynx	140-149.X
Malignant neoplasm of the digestive organs and peritoneum	150-159.X
Malignant neoplasm of the respiratory and intrathoracic organs	160-165.X
Malignant neoplasm of the bone, connective tissue, skin, and breast	170-176.X
Malignant neoplasm of the genitourinary organs	179-189.X
Malignant neoplasm of other and unspecified sites	190-199.X
Malignant neoplasm of lymphatic and hematopoietic tissue	200-208.XX
Neuroendocrine tumors	209.XX

Patient demographics included age, sex, race, and ethnicity. Charlson comorbidities and other relevant diagnoses, as defined by ICD-9-CM codes, were collected for the year prior to the CDI encounter (Table 4.2). The Charlson comorbidity score was calculated as modified by Deyo et al.[75]

Table 4.2. Study comorbidity definitions

Comorbidity	**ICD-9-CM code(s)**
Hypertension	401-405
Dyslipidemia	272
Obesity	278
Myocardial infarction	410, 412
Congestive heart failure	428
Peripheral vascular disease	441, 443.9, 785.4, V43.4
Cerebrovascular disease	430-438
Dementia	290
COPD	490-496, 500-505, 506.4
Rheumatologic disease	710.0-710.1, 710.4, 714.0-714.2, 714.81, 725
Peptic ulcer disease	531.0-531.9, 532.0-532.9, 533.0-533.9, 534.0-534.9
Liver disease	571.2, 571.4, 571.5, 571.6, 572.2-572.8, 456.0-456.21
Diabetes	250.0-250.3, 250.4, 250.5, 250.6, 250.7, 250.8, 250.9
Renal disease	582, 583, 585, 586, 588
HIV/AIDS	42-44, V08
Bacteremia	790.7
Pneumonia	480.0-483.99, 485–487
Skin infection	680-686
Endocarditis	421.0, 421.1, 421.9, 424.9
Urinary tract infection	590-599
Device-related infection	996.31, 996.62, 996.64, 999.31
Acute respiratory infection	460-466
GERD	530.11, 530.81
Transplant	V42, E878.0
Inflammatory bowel disease	555, 556
Irritable bowel syndrome	564.1
Bacteremia	790.7
Pneumonia	480.0-483.99, 485–487
Skin infection	680-686
Intra-abdominal infection	540–543, 562, 567, 569, 574–577
Urinary tract infection	590-599
Device-related infection	996.31, 996.62, 996.64, 999.31
Acute respiratory infection	460-466
Endocarditis	421.0, 421.1, 421.9, 424.9
Shock	639.5, 785.52, 785.59
Sepsis/septicemia	020.2, 038.0-038.9, 995.91, 995.92
Prolonged ileus	560.1

Megacolon	558.2, 564.7
Acute renal failure	584, 586

Principal CDI was defined as ICD-9-CM code 008.45 in the first position. This often indicates that CDI was the primary contributor to hospitalization. Secondary CDI was defined as ICD-9-CM code 008.45 in any position except first. CDI was also characterized by type. Community-onset CDI (CO-CDI) was defined based upon the presence of CDI therapy initiated in the outpatient setting or on days 1 or 2 of hospitalization. Community-onset, healthcare facility-associated CDI (CO-HCFA-CDI) was defined the same way, with the addition of a hospitalization in the prior 90 days. Lastly, healthcare facility-onset CDI was defined as CDI therapy beginning on day 3 or later of hospitalization.

Concomitant infections were collected that occurred during an encounter (between CDI episode start date and end of CDI therapy for CDI patients and during hospitalization for control group), including: bacteremia, pneumonia, skin infection, intra-abdominal infection, urinary tract infection, device-related infection, endocarditis, and acute respiratory infection. Other markers of CDI severity that occurred during an encounter were also captured, including sepsis/septicemia, shock, megacolon, prolonged ileus, perforated intestine, acute renal failure, and ICU admission.

Prior and concomitant non-CDI antibiotics (excludes oral vancomycin, metronidazole, fidaxomicin, rifaximin, and nitazoxanide), gastric acid suppressant (GAS) drugs (antacids, histamine-2 receptor antagonists [H2RAs], proton pump inhibitors [PPIs]), and narcotics were collected. Prior use was defined as any use in the 90 days prior to the encounter and concomitant use was defined as any use during or within 60

days following the encounter. The 60-day follow-up period for concomitant medication use was chosen because this time period is likely to capture the majority of medication use between initial CDI and recurrence; recurrent CDI is most common within one to three weeks post-treatment discontinuation, but late recurrences are also common.[76]

For aim 3, CDI therapy was defined as receipt of either oral vancomycin or metronidazole (intravenous or oral). Fidaxomicin was used very infrequently (<1% of the population); therefore, comparative-effectiveness studies with this antibiotic were not feasible. For comparisons between metronidazole and vancomycin, patients were limited to those who received only monotherapy with one of these agents.

DEPENDENT VARIABLES

For aim 1 only, CDI was the primary dependent variable. CDI was defined as stated in the study population section and was compared to a non-CDI control group.

All-cause 30-day mortality was our primary outcome for aims 2 and 3. Hospital LOS was also assessed. We defined hospital LOS as a dichotomous (hospital LOS ≥14 versus <14 days) to facilitate logistic regression modeling. Another important dependent variable included CDI recurrence. Recurrent CDI typically occurs within one to three weeks post-treatment discontinuation, but late recurrences, occurring up to 60 days post-treatment discontinuation, are frequent. The mean relapse time is approximately 14.5 days, whereas mean reinfection time is 42.5 days.[76] We chose 60-day recurrence as our primary dependent variable because it is likely to capture the majority of CDI recurrences. This definition and has been used as the primary outcome in other studies evaluating CDI recurrence risk.[77]

DATA AND STATISTICAL ANALYSIS

Data extraction and variable creation were conducted using SAS Version 9.2® (SAS Corp., Cary, NC, USA). All other data and statistical analyses were conducted using JMP 10.0® (SAS Corp., Cary, NC, USA).

Specific Aim 1

In this case-control design that included all CDI patients and controls, all independent and dependent variables were first presented descriptively. Continuous variables were presented as means, standard deviations, medians, and interquartile ranges. Categorical variables were presented as the number and percentage of subjects in each category. For baseline characteristics (e.g., gender, race, ethnicity), we included a missing category. Other variables that were absent from the medical chart (e.g., comorbidities, medications) were assumed to have not occurred.

We first compared independent variables, including cancer diagnoses, between groups using the chi-square test. Next, we conducted a multivariable logistic regression test using CDI as the dependent variable, cancer as the independent variable, and 28 covariates. Covariates included age, gender, race & ethnicity, fiscal year of visit, hypertension, dyslipidemia, obesity, myocardial infarction, paraplegia/hemiplegia, congestive heart failure, perivascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, rheumatologic disease, liver disease, diabetes, renal disease, HIV/AIDS, GERD, transplant, inflammatory bowel diseases, irritable bowel

syndrome, prior antibiotics, prior gastric acid suppressants, prior narcotics, prior anti-diarrheals, and prior bowel prep. To assess the risk of CDI by cancer type, we repeated the above procedures to assess each cancer type as an independent risk factor for CDI.

Specific Aim 2

In this retrospective cohort study, the study population was limited to CDI patients only (exclusive of controls). Health outcomes, including 30-day mortality, hospital LOS ≥14 days, and 60-day CDI recurrence were compared between CDI patients with and without cancer using the chi-square test. Next, we conducted a series of multivariable logistic regression tests using each health outcome as the dependent variable, cancer as the independent variable, and 58 covariates. Covariates included age, gender, race & ethnicity, fiscal year of visit, principal CDI, CDI surveillance definition, hypertension, dyslipidemia, obesity, myocardial infarction, congestive heart failure, perivascular disease, cerebrovascular disease, paraplegia/hemiplegia, dementia, chronic obstructive pulmonary disease, rheumatologic disease, liver disease, diabetes, renal disease, HIV/AIDS, GERD, transplant, inflammatory bowel diseases, irritable bowel syndrome, prior medications (antibiotics, gastric acid suppressants, narcotics, anti-diarrheals, prior bowel prep), concomitant infections (bacteremia, skin infection, pneumonia, UTI, intra-abdominal infection, endocarditis, respiratory tract infection), individual severity indicators, and concomitant medications (antibiotics, gastric acid

suppressants, narcotics, anti-diarrheals, prior bowel prep), including CDI therapies (metronidazole, vancomycin, fidaxomicin, rifaximin, nitazoxanide, probiotics).

Specific Aim 3

In this retrospective cohort study, the study population was limited to CDI patients with cancer only and those who received monotherapy with either metronidazole or oral vancomycin. Health outcomes, including 30-day mortality, hospital LOS ≥14 days, and 60-day CDI recurrence were compared between CDI patients with and without cancer using the chi-square test for dichotomous outcomes and the Wilcoxon rank sum test for hospital LOS. Next, we conducted a series of multivariable logistic regression tests using each health outcome as the dependent variable, cancer as the independent variable, and 52 covariates. Covariates included age, gender, race & ethnicity, fiscal year of visit, principal CDI, CDI surveillance definition, hypertension, dyslipidemia, obesity, myocardial infarction, congestive heart failure, perivascular disease, cerebrovascular disease, paraplegia/hemiplegia, dementia, chronic obstructive pulmonary disease, rheumatologic disease, liver disease, diabetes, renal disease, HIV/AIDS, GERD, transplant, inflammatory bowel diseases, irritable bowel syndrome, prior medications (antibiotics, gastric acid suppressants, narcotics, anti-diarrheals, prior bowel prep), concomitant infections (bacteremia, skin infection, pneumonia, UTI, intra-abdominal infection, endocarditis, respiratory tract infection), individual severity indicators, and

concomitant medications (antibiotics, gastric acid suppressants, narcotics, anti-diarrheals, prior bowel prep).

Lastly, we validated the results of the logistic regression model using a propensity score-matched cohort. Specifically, logistic regression was used to generate propensity scores using the treatment (metronidazole versus vancomycin) as the dependent variable and the following 28 covariates: Covariates included age, gender, race & ethnicity, fiscal year of visit, hypertension, dyslipidemia, obesity, myocardial infarction, congestive heart failure, perivascular disease, cerebrovascular disease, paraplegia/hemiplegia, dementia, chronic obstructive pulmonary disease, rheumatologic disease, liver disease, diabetes, renal disease, HIV/AIDS, GERD, transplant, inflammatory bowel diseases, irritable bowel syndrome, and prior medications (antibiotics, gastric acid suppressants, narcotics, anti-diarrheals, prior bowel prep). Propensity scores were then matched 1:1 using nearest neighbor matching without replacement and a caliper of 0.001. Following matching, health outcomes were compared between cancer and non-cancer groups using the chi-square test.

CHAPTER 5

RESULTS

General Population Characteristics

Overall 26,149 patients met study inclusion criteria for CDI and another 52,298 were included as non-CDI controls. Table 5.1 describes the patients' baseline characteristics. CDI patients were predominately elderly (median age 67 years), male (95.9%), and White (71.8%). The median (IQR) Charlson comorbidity score was 3 (1-5). The most common comorbidities included: hypertension (77.5%), diabetes (40.3%), dyslipidemia (54.7%), COPD (37.7%), and cancer (26.6%). CDI patients were commonly exposed to other medications prior to the episode including non-CDI antibiotics (55.4%) and GAS drugs (55.7%).

Given the large sample size, there were statistically significant differences between the CDI and control cohort for all independent variables tested. Patients with CDI tended to have higher rates of comorbidities and medication use prior to cohort inclusion, as seen in the higher median Charlson score in the CDI cohort compared to the control group (3 vs. 1; $p<0.0001$). Other notable differences included older age and more prior hospitalizations among CDI patients and a higher proportion of cardiovascular, metabolic, inflammatory diseases. Prior medication use was also significantly more common among CDI patients compared to controls.

Table 5.1 Patient baseline characteristics in the CDI and control cohorts

Characteristic	CDI (n=26,149)	Control (n=52,298)	P-value
Age (years), median (IQR)	67 (60-78)	62 (53-72)	<0.0001
Male sex, %	95.9	93.9	<0.0001
Hispanic ethnicity, %	5.3	6.0	<0.0001
White race, %	71.8	69.0	<0.0001
Prior hospitalization, %	49.0	16.0	<0.0001
Hypertension	77.5	56.8	<0.0001
Dyslipidemia	54.7	44.6	<0.0001
Obesity	16.4	14.7	<0.0001
Myocardial infarction	11.1	3.7	<0.0001
Congestive heart failure	26.1	8.6	<0.0001
Peripheral vascular disease	18.8	8.5	<0.0001
Cerebrovascular disease	19.2	9.5	<0.0001
Dementia	3.8	1.5	<0.0001
COPD	37.7	20.5	<0.0001
Peptic ulcer disease	4.6	1.6	<0.0001
Liver disease	7.0	2.2	<0.0001
Diabetes	40.3	26.7	<0.0001
Renal disease	27.7	8.1	<0.0001
Cancer	26.6	15.3	<0.0001
Metastasis	7.7	2.9	<0.0001
Oral	0.0	0.9	<0.0001
Digestive	6.0	3.2	<0.0001
Respiratory	4.7	3.2	<0.0001
Bone, skin, breast	5.2	3.4	<0.0001
Genitourinary	11.0	7.4	<0.0001
Lymphatic/hematologic	2.9	1.5	<0.0001
Neuroendocrine	0.2	0.1	0.0003
Other	6.9	3.8	<0.0001
HIV/AIDS	1.8	0.8	<0.0001
GERD	26.7	23.1	<0.0001
Transplant	1.9	< 0.1	<0.0001
Inflammatory bowel disease	2.2	0.8	<0.0001
Irritable bowel syndrome	1.1	0.9	0.0018
Charlson score, median (IQR)	3 (2-6)	1 (0-3)	<0.0001
Prior antibiotics	55.4	21.5	<0.0001
Prior GAS drugs	55.7	31.2	<0.0001
Prior narcotics	38.0	21.2	<0.0001

SPECIFIC AIM 1: DEFINE THE RISK OF CDI ASSOCIATED WITH A CANCER DIAGNOSIS, COMPARED TO A GROUP OF NON-CDI CONTROLS

Hypothesis 1.1: The risk of CDI is greater in patients with a cancer diagnosis.

In bivariable analyses, the proportion of patients with a prior diagnosis of cancer was significantly higher in the CDI cohort (26.6%) compared to the control cohort (15.3%) (Table 5.1). In the multivariable model, cancer was an independent predictor of CDI (OR 1.41; 95% CI 1.35-1.47); therefore, we accept our alternative hypothesis that the risk of CDI is greater in patients with cancer. Despite this, cancer was not as strong of a predictor compared to other factors. A diagnosis code for transplant was the strongest predictor of CDI (OR 39.9; 95% CI 23.26-68.56), followed by paraplegia/hemiplegia (OR 3.73; 95% CI 3.30-4.22), inflammatory bowel disease (OR 3.69; 95% CI 3.20-4.26), liver disease (OR 2.96; 95% CI 2.72-3.22), HIV/AIDS (OR 2.73; 95% CI 2.34-3.17), and prior antibiotic use (OR 2.32; 95% CI 2.23-2.42) (Table 5.2).

Table 5.2 Independent risk factors for CDI

Characteristic	OR (95% CI)
Transplant	39.9 (23.26 - 68.56)
Paraplegia/hemiplegia	3.73 (3.30 - 4.22)
Inflammatory bowel disease	3.69 (3.20 - 4.26)
HIV/AIDS	2.73 (2.34 - 3.17)
Liver disease	2.96 (2.72 - 3.22)
Prior antibiotics	2.32 (2.23 - 2.42)
Renal disease	2.17 (2.07 - 2.28)
Prior Hospitalization	2.05 (1.97 - 2.14)
Peptic Ulcer Disease	2.05 (1.85 - 2.27)
Dementia	1.70 (1.52- 1.90)
Congestive heart failure	1.64 (1.56 - 1.73)
Myocardial Infarction	1.54 (1.43 - 1.65)
Irritable bowel syndrome	1.51 (1.27 - 1.78)
Rheumatologic disease	1.45 (1.28 - 1.63)
COPD	1.42 (1.37 - 1.48)
Cancer	**1.41 (1.35 - 1.47)**
Hypertension	1.39 (1.33 - 1.45)
Age > 65 years	1.38 (1.33 - 1.44)
Peripheral vascular disease	1.30 (1.23 - 1.37)
Cerebrovascular disease	1.27 (1.20 - 1.33)
Prior GAS	1.18 (1.14 - 1.23)
Prior narcotics	1.16 (1.12 - 1.21)
Female sex	1.10 (1.01 - 1.19)
non-Hispanic ethnicity	1.10 (1.02 - 1.19)
White race	1.07 (1.02 - 1.12)
Diabetes	1.07 (1.03 - 1.12)

Hypothesis 1.2: Patients with hematologic malignancy will have a higher risk of CDI compared to non-hematologic cancers.

In bivariable analysis, the proportion of patients with each cancer types (with the exception of oral cancers) was higher among the CDI cohort compared to the control cohort (Table 5.2). In multivariable models, cancer with metastasis was the strongest, statistically significant predictor of CDI, followed by lymphatic/hematologic cancers (Table 5.3). Interestingly, genitourinary, respiratory, and other cancers were inverse predictors of CDI.

Table 5.3 Independent risk factors for CDI by cancer type

Characteristic	OR (95% CI)
Metastasis	**4.68 (4.02-5.45)**
Neuroendocrine	1.38 (0.83-2.30)
Lymphatic/hematologic	**1.27 (1.03-1.31)**
Digestive	1.06 (0.97-1.16)
Bone, skin, breast	1.02 (0.93-1.11)
Genitourinary	**0.93 (0.87-0.99)**
Respiratory	**0.75 (0.68-0.83)**
Other	**0.32 (0.27-0.37)**
Oral*	--

*Removed due to model instability
Note: bold indicates statistical significance at $p<0.05$

SPECIFIC AIM 2: COMPARE CDI CLINICAL OUTCOMES OF PATIENTS WITH AND WITHOUT CANCER

Hypothesis 2.1: Patients with cancer will have higher risk of 30-day mortality, 60-day CDI recurrence, and hospital LOS compared to non-cancer patients.

Among patients with CDI, 7,538 (28.8%) were diagnosed with cancer. Patients with cancer were more likely to be older, have HCFO-CDI, and have more comorbidity (Table 5.4). CDI severity was relatively similar between groups. Prior and concomitant medication use was significantly more common among patients with cancer.

Table 5.4 Baseline characteristics among CDI patients with and without cancer

Characteristic	No Cancer (n=18,611)	Cancer (n=7,538)	P-value
Age (years), median (IQR)	66 (59-78)	70 (63-79)	<0.0001
Male sex, %	95.3	97.3	<0.0001
Race & ethnicity, %			0.0007
Non-Hispanic White	66.1	66.6	
Non-Hispanic Black	21.2	20.8	
Hispanic	5.7	4.7	
Other	4.3	4.6	
Missing	2.8	3.3	
Principal CDI diagnosis, %	28.9	26.3	<0.0001
CDI type, %			<0.0001
CA-CDI	21.2	14.4	
CO-HCFA-CDI	20.0	21.9	
HCFO-CDI	58.8	63.7	
Comorbidities, %			
Hypertension	77.4	78.3	0.0638
Dyslipidemia	53.9	56.2	0.0004
Obesity	17.0	15.3	0.0002
Myocardial infarction	11.8	10.2	<0.0001
Congestive heart failure	28.0	23.0	<0.0001
Peripheral vascular disease	20.1	17.8	<0.0001
Cerebrovascular disease	20.1	18.0	<0.0001
Dementia	4.0	3.1	<0.0001
COPD	36.5	41.3	<0.0001
Rheumatologic disease	2.8	2.6	0.3770
Peptic ulcer disease	4.5	5.0	0.0522
Liver disease	7.6	6.0	<0.0001
Diabetes	42.8	36.8	<0.0001
Renal disease	28.6	27.6	0.0797
HIV/AIDS	2.1	1.4	0.0002
GERD	26.7	28.1	0.0167
Transplant	1.9	2.2	0.1694
Inflammatory bowel disease	2.8	1.6	<0.0001
Irritable bowel syndrome	1.3	0.7	<0.0001
Charlson score, median (IQR)	3 (1-5)	6 (4-9)	<0.0001

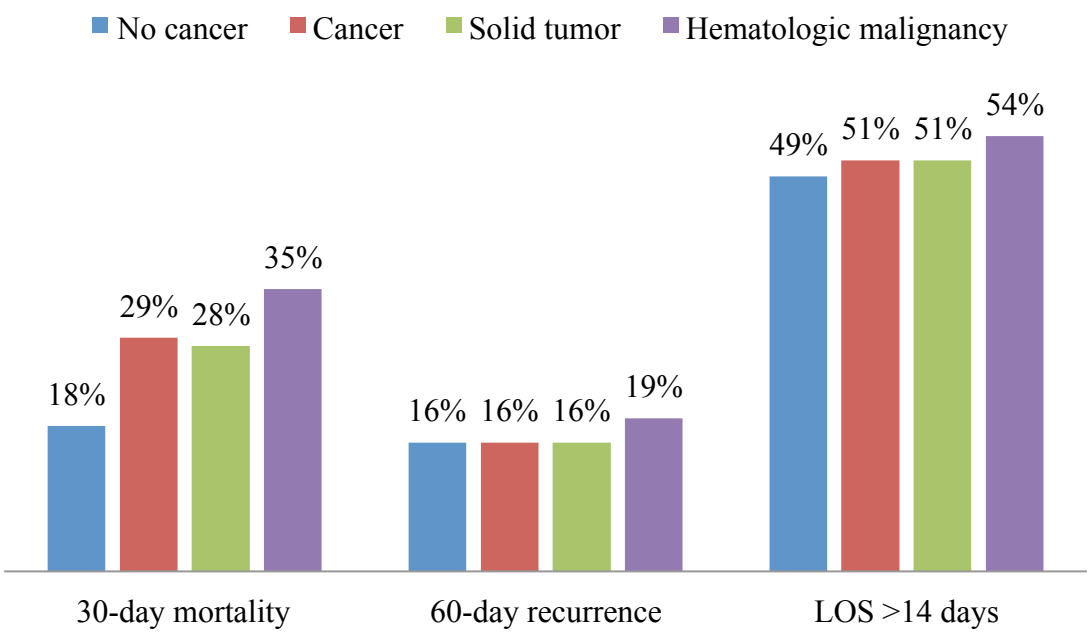
Table 5.4 Baseline characteristics among CDI patients (continued)

Characteristic	No Cancer (n=18,611)	Cancer (n=7,538)	P-value
Concomitant infections, %			
Bacteremia	6.8	7.4	0.0826
Pneumonia	22.6	24.1	0.0038
Skin infection	12.0	8.2	<0.0001
Intra-abdominal infection	6.3	5.3	0.0007
Device-related infection	3.3	3.3	0.7436
Acute respiratory infection	3.5	3.2	0.1708
Endocarditis	1.2	0.7	0.0004
Urinary tract infection	1.3	3.0	<0.0001
CDI severity indicators, %			
ICU admission	3.4	3.0	0.0446
Sepsis/septicemia	17.3	18.7	0.0046
Shock	5.2	5.1	0.8410
Acute renal failure	30.7	30.9	0.6496
Megacolon	0.3	0.3	0.8332
Prolonged ileus	3.9	4.5	0.0130
Perforated intestine	0.5	0.7	0.0145
WBC ≥15,000 cells/μL	38.4	41.1	<0.0001
CRP ≥160 mg/L	1.8	1.4	0.0072
Albumin <2.5 g/dL	30.9	37.6	<0.0001
Medications, %			
Prior antibiotics	54.4	62.5	<0.0001
Prior GAS drugs	54.9	62.2	<0.0001
Prior narcotics	35.3	47.8	<0.0001
Prior anti-diarrheals	6.7	10.1	<0.0001
Prior bowel prep	14.0	19.9	<0.0001
Concomitant antibiotics	73.7	78.8	<0.0001
Concomitant GAS drugs	78.0	82.2	<0.0001
Concomitant narcotics	47.7	59.7	<0.0001
Concomitant anti-diarrheals	10.5	13.3	<0.0001
Concomitant bowel prep	18.3	22.2	<0.0001

In bivariable analyses, patients with cancer experienced higher rates of 30-day mortality (29.0% vs. 17.7%, p<0.0001) compared to non-cancer patients (Figure 5.1). There was not a significant difference in 60-day recurrence (16.2% vs. 16.0%, p=0.7960) or hospital LOS ≥14 days (51.3% vs. 48.5%, p=0.3827) between cancer and non-cancer patients. In multivariable models, cancer was a significant predictor of 30-day mortality (OR 1.44; 95% CI 1.33-1.55), but not of 60-day recurrence (OR 1.00; 95% CI 0.91-1.13) or hospital LOS ≥14 days (OR 0.99; 95% CI 0.92-1.12).

When limited to CDI patients with cancer, the majority of patients were diagnosed with a solid cancer (89.9%) compared to hematologic malignancy (10.1%). In bivariable analyses, hematologic malignancy patients experienced higher rates of 30-day mortality (35.1% vs. 28.3%, p<0.0001) compared to solid tumor patients (Figure 5.1). There was not a significant difference in 60-day recurrence (19.1% vs. 15.8%, p=0.4532) or hospital LOS ≥14 days (54.5% vs. 51.0%, p=0.3235) between hematologic malignancy and solid tumor patients. In multivariable models, hematologic malignancy was a significant predictor of 30-day mortality (OR 1.85; 95% CI 1.56-2.19), but not of 60-day recurrence (OR 1.22; 95% CI 0.95-1.58) or hospital LOS ≥14 days (OR 1.06; 95% CI 0.90-1.26).

Figure 5.1 Clinical outcomes by cancer type



SPECIFIC AIM 3: COMPARE CDI CLINICAL OUTCOMES AMONG PATIENTS WHO RECEIVE METRONIDAZOLE OR VANCOMYCIN

Hypothesis 3.1: Patients who receive oral metronidazole will have higher risk for 30-day mortality, 60-day CDI recurrence, and hospital LOS compared to patients who receive oral vancomycin.

A total of 3,968 (80.6%) CDI patients received oral metronidazole monotherapy and 953 (19.4%) received oral vancomycin monotherapy (Table 5.5). Prior to propensity score matching, patients treated with vancomycin were more likely to have a principal CDI diagnosis and have community-onset CDI. Importantly, vancomycin-treated patients had more severe disease, as indicated by higher rates of sepsis, shock, acute renal failure, complications, and abnormal laboratory values.

In the unmatched cohorts, 30-day mortality was similar between patients treated with metronidazole (27.2%) compared to vancomycin (29.3%) (OR 1.12; 95% CI 0.91-1.36) (Figure 5.2). Interestingly, vancomycin was associated with a significantly higher risk of 60-day CDI recurrence (23.3% vs. 13.7%; OR 1.70; 95% CI 1.27-2.27) and hospital LOS $\geq$ 14 days (45.4% vs. 42.6%; OR 1.70; 95% CI 1.39-2.07).

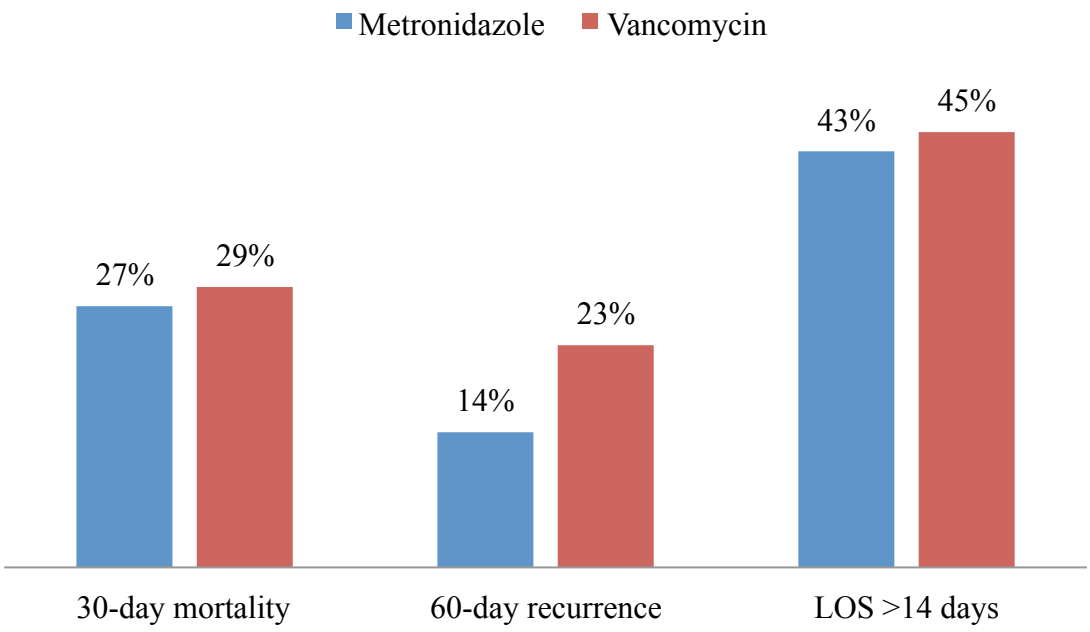
Table 5.5 Baseline characteristics of cancer cohort

Characteristic	Metronidazole (n=3,968)	Vancomycin (n=953)	P-value
Age (years), median (IQR)	70 (63-79)	69 (63-79)	0.9171
Male sex, %	96.9	98.0	0.0465
Race & ethnicity, %			0.0052
Non-Hispanic White	66.3	65.6	
Non-Hispanic Black	20.7	19.5	
Hispanic	4.1	7.0	
Other	5.5	4.4	
Missing	3.4	3.5	
Principal CDI diagnosis, %	23.2	29.2	0.0002
CDI type, %			<0.0001
CA-CDI	15.7	20.7	
CO-HCFA-CDI	23.1	28.9	
HCFO-CDI	61.2	50.5	
Comorbidities, %			
Hypertension	77.2	79.0	0.2392
Dyslipidemia	54.9	60.7	0.0014
Obesity	15.1	14.9	0.8641
Myocardial infarction	9.4	9.7	0.7920
Congestive heart failure	22.4	21.1	0.3878
Peripheral vascular disease	16.4	18.5	0.1349
Cerebrovascular disease	17.1	18.2	0.4257
Dementia	3.2	2.4	0.2195
COPD	41.7	39.8	0.2680
Rheumatologic disease	2.4	2.6	0.6832
Peptic ulcer disease	5.3	5.0	0.7029
Liver disease	5.2	7.3	0.0110
Diabetes	35.5	38.4	0.0900
Renal disease	25.1	31.8	<0.0001
Solid tumor	90.7	89.3	0.1916
Metastases	28.4	27.0	0.3917
HIV/AIDS	1.2	1.6	0.3467
GERD	27.4	31.4	0.0150
Transplant	1.8	2.9	0.0266
Inflammatory bowel disease	1.3	2.3	0.0266
Irritable bowel syndrome	0.8	0.3	0.1020
Charlson score, median (IQR)	6 (3-9)	6 (4-9)	0.0942

Table 5.5 Baseline characteristics of cancer cohort (continued)

Characteristic	Metronidazole (n=3,968)	Vancomycin (n=953)	P-value
Concomitant infections, %			
Bacteremia	5.8	5.2	0.4695
Pneumonia	20.8	21.1	0.8515
Skin infection	7.3	5.2	0.0187
Intra-abdominal infection	4.8	3.0	0.0142
Device-related infection	2.6	2.5	0.8920
Acute respiratory infection	2.8	1.0	0.0005
Endocarditis	0.4	0.5	0.6150
Urinary tract infection	2.9	2.2	0.2122
CDI severity indicators, %			
ICU admission	2.9	2.9	0.9143
Sepsis/septicemia	11.9	26.1	<0.0001
Shock	2.4	8.8	<0.0001
Acute renal failure	25.2	35.7	<0.0001
Megacolon	0.1	0.3	0.0926
Prolonged ileus	3.2	5.9	0.0002
Perforated intestine	0.3	0.9	0.0138
WBC ≥15,000 cells/μL	33.9	50.9	<0.0001
CRP ≥160 mg/L	0.8	2.0	0.0037
Albumin <2.5 g/dL	30.9	47.7	<0.0001
Medications, %			
Prior antibiotics	61.2	62.2	0.5457
Prior GAS drugs	60.6	61.8	0.4969
Prior narcotics	45.9	47.5	0.3615
Prior anti-diarrheals	9.5	9.1	0.7411
Prior bowel prep	19.1	22.5	0.0201
Concomitant antibiotics	75.7	76.1	0.7855
Concomitant GAS drugs	80.3	79.7	0.6797
Concomitant narcotics	57.1	57.2	0.9413
Concomitant anti-diarrheals	12.7	9.9	0.0138
Concomitant bowel prep	21.1	23.7	0.0801
CDI therapies, %			
Fidaxomicin	0.02	0.9	<0.0001
Rifaximin	0.6	1.3	0.0241
Probiotics	18.0	18.4	0.7766

Figure 5.2 Comparative-effectiveness of metronidazole and vancomycin on CDI health outcomes in the unmatched cohort



After propensity score matching, a total of 800 CDI patients were included each in the metronidazole and vancomycin groups (Table 5.6). Matching resulted in statistically similar baseline characteristics, comorbidities, CDI severity, and medication use.

In the matched cohorts, 30-day mortality was similar between patients treated with metronidazole (26.3%) compared to vancomycin (27.8%) (OR 1.08; 95% CI 0.87-1.34) (Figure 5.3). Similar to the unmatched cohorts, vancomycin was associated with a significantly higher risk of 60-day CDI recurrence (23.1% vs. 15.2%; OR 1.67; 95% CI 1.23-2.27) and hospital LOS ≥ 14 days (44.8% vs. 35.5%; OR 1.37; 95% CI 1.05-1.78).

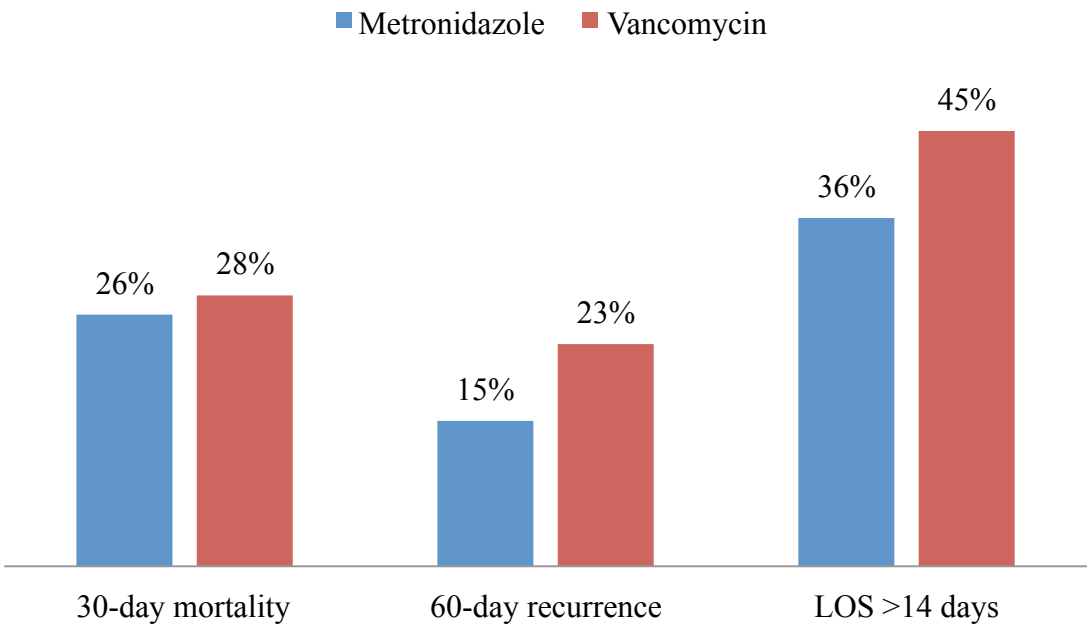
Table 5.6 Baseline characteristics of propensity score-matched cancer cohort

Characteristic	Metronidazole (n=800)	Vancomycin (n=800)	P-value
Age (years), median (IQR)	69 (63-79)	69 (63-79)	0.888
Male sex, %	98.0	97.6	0.608
Race & ethnicity, %			0.068
Non-Hispanic White	62.9	66.4	
Non-Hispanic Black	23.8	18.1	
Hispanic	5.6	6.9	
Other	3.9	4.9	
Missing	3.9	3.8	
Principal CDI diagnosis, %	27.1	28.1	0.695
CDI type, %			0.314
CA-CDI	20.8	19.8	
CO-HCFA-CDI	25.3	28.6	
HCFO-CDI	54.0	51.6	
Comorbidities, %			
Hypertension	78.6	78.6	1.000
Dyslipidemia	56.4	60.0	0.171
Obesity	14.8	15.1	0.833
Myocardial infarction	10.1	9.5	0.674
Congestive heart failure	20.4	21.4	0.623
Peripheral vascular disease	17.3	18.0	0.694
Cerebrovascular disease	20.3	17.0	0.095
Dementia	2.3	2.1	0.864
COPD	40.8	39.1	0.507
Rheumatologic disease	2.8	2.8	1.000
Peptic ulcer disease	5.6	5.4	0.826
Liver disease	7.0	6.5	0.690
Diabetes	35.4	37.1	0.467
Renal disease	29.8	30.0	0.913
Solid tumor	10.4	10.1	0.869
Metastases	27.6	27.9	0.911
HIV/AIDS	1.8	1.5	0.693
GERD	31.3	31.0	0.914
Transplant	2.8	2.9	0.880
Inflammatory bowel disease	1.5	1.9	0.560
Irritable bowel syndrome	0.4	0.4	1.000
Charlson score, median (IQR)	6 (4-9)	6 (4-9)	0.844

Table 5.6 Baseline characteristics of propensity score-matched cancer cohort (continued)

Characteristic	Metronidazole (n=800)	Vancomycin (n=800)	P-value
Concomitant infections, %			
Bacteremia	4.9	5.1	0.819
Pneumonia	21.2	20.5	0.712
Skin infection	6.1	5.5	0.593
Intra-abdominal infection	3.3	3.3	1.000
Device-related infection	1.5	2.1	0.349
Acute respiratory infection	1.0	1.0	1.000
Endocarditis	0.6	0.4	0.478
Urinary tract infection	2.5	2.1	0.618
CDI severity indicators, %			
ICU admission	2.0	2.0	1.000
Sepsis/septicemia	19.9	19.1	0.705
Shock	5.1	4.0	0.281
Acute renal failure	32.1	31.0	0.628
Megacolon	0.1	0.0	0.317
Prolonged ileus	4.1	4.0	0.899
Perforated intestine	0.3	0.9	0.095
WBC ≥15,000 cells/μL	42.8	45.3	0.314
CRP ≥160 mg/L	1.6	1.3	0.529
Albumin <2.5 g/dL	44.9	43.4	0.546
Medications, %			
Prior antibiotics	63.3	61.1	0.381
Prior GAS drugs	62.9	61.0	0.440
Prior narcotics	48.8	47.5	0.617
Prior anti-diarrheals	8.3	9.4	0.427
Prior bowel prep	23.1	22.0	0.590
Concomitant antibiotics	75.0	74.4	0.774
Concomitant GAS drugs	80.1	79.4	0.709
Concomitant narcotics	59.8	57.1	0.287
Concomitant anti-diarrheals	10.5	10.0	0.742
Concomitant bowel prep	23.6	23.9	0.907
CDI therapies, %			
Rifaximin	0.8	1.0	0.591
Probiotics	17.0	17.3	0.894

Figure 5.3 Comparative-effectiveness of metronidazole and vancomycin on CDI health outcomes in the propensity score-matched cohort



CHAPTER 6

DISCUSSION AND CONCLUSIONS

Specific Aim 1

In this aim, we explored the impact of cancer diagnosis on CDI risk. We found that cancer was associated with a 1.4 fold increased risk for CDI compared to no cancer diagnosis. Importantly, we also found that certain cancer diagnoses more strongly increased CDI risk. Specifically, patients with metastases or lymphatic/hematologic cancers were at highest risk compared to other cancer types.

Our findings that cancer increases risk for CDI are in-line with prior studies. While few other studies have assessed cancer as an independent risk factor for CDI, multiple studies have documented significantly higher rates of CDI among cancer patients. In our prior work analyzing U.S. community hospitals, the incidence of CDI among cancer patients was 1.4 times higher than non-cancer patients.[37]

The mechanism by which cancer increases the risk for CDI is likely multifaceted. First, cancer patients are often exposed to the health care system to a greater degree, which increases their likelihood of acquired *C. difficile* spores from the environment. Prior studies have found that hospitalized patients (4-29%) have significantly higher *C. difficile* colonization rates compared to health adults (0-15%).[1] They are also more likely to develop clinical infection after spore acquisition due to several reasons. Cancer patients are often exposed to medications that disrupt the normal gut microbiota, such as antibiotics and chemotherapeutic agents. Dysbiosis then reduces the host's ability to protect against pathogens, like *C. difficile*. Furthermore, cancer is associated with

immunosuppression; thus, cancer patients may not be able to mount an adequate immune response to *C. difficile* toxins once spores begin to germinate.

It's important to note that cancer was not the primary risk factor for CDI. Transplant was the strongest predictor of CDI, followed by paraplegia/hemiplegia, inflammatory bowel disease, liver disease, HIV/AIDS, and prior antibiotic use. Some of these are well-known risk factors, while others have not been previously reported.

HSCT patients are traditionally one of the highest risk groups for CDI,[39] likely due to immunosuppression and health care exposures. Prior antibiotic use is another classic risk factor for CDI due to its gut microbiome-mediating effects,[14] which reduce the host's ability for colonization resistance. Lastly, patients with inflammatory bowel disease have been previously reported to be at higher risk for CDI. This is likely due to colonic inflammation and significant differences in host gut microbiome in IBD patients compared to non-IBD patients.[78]

One of the more interesting risk factors identified in this study was paraplegia/hemiplegia. To our knowledge, this has not been reported in prior studies. This could be, in part, due to the generally low prevalence of this diagnosis in the general population, but higher prevalence among veterans. We hypothesize that the risk for these patients may be related to healthcare exposures (hospitalizations, enteral feedings) or limited mobility, which may impact overall gut health.

Next, in this study we found that certain cancer patients were at higher risk for CDI compared to others. Patients with metastases were especially at higher risk. This is likely due to greater degree of healthcare exposures and immunosuppression due to disease and drug therapy. To our knowledge, this is the first study to identify this specific

relationship; therefore, further studies are needed to elucidate the mechanisms for this relationship.

Hematologic malignancies were also associated with increased CDI risk. This is consistent with our prior work that demonstrated that the incidence of CDI among hematologic cancers was more than double that of solid cancer types.[37] A retrospective review of leukemia patients revealed that CDI occurred in 7% of all cycles of myelosuppressive chemotherapy.[59] Lastly, an analysis of 134 patients found that CDI occurred in 18% of patients with acute myeloid leukemia and in 9% of all treatment courses.[79] The relationship is likely due to healthcare exposures as described in the background. Patients with blood cancers might receive antibiotics at a higher rate due to a higher incidence of neutropenic fever resulting from cytotoxic chemotherapy and direct effects on host immunity.[50] Furthermore, patients with blood cancers tend to have a longer length of stay during hospitalizations compared to solid tumor patients.[80] Lastly, hematologic malignancies have the therapeutic option of HSCT. When comparing HSCT recipients versus other cancer patients, Chopra et al.[39] reported HSCT recipients to have 1.4 times higher CDI rates. It is hypothesized these differences are due to chemotherapy regimens and antibiotic use leading up to transplantation, in addition to prolonged hospital stay.[47,52,53] The distinction between hematologic malignancy versus solid tumor is of importance in CDI prevention and treatment. Due to the increased risk associated with hematologic malignancies, more diligent antimicrobial stewardship may be warranted along with potentially more aggressive CDI treatment. To our knowledge, this is the first study to compare specific cancer types and CDI risk.

Specific Aim 2

In this aim, we compared CDI clinical outcomes between cancer and non-cancer patients. We found that a cancer diagnosis was associated with a 1.4 fold increase in risk for 30-day mortality compared to no cancer diagnosis. Cancer was not associated with risk differences in 60-day recurrence or hospital LOS though. Important, hematologic cancers resulted in significantly higher risk for mortality compared to solid cancers.

This was one of the first studies to evaluate the impact of cancer on CDI health outcomes. In our prior study of the U.S. National Hospital Discharge Surveys, cancer patients with CDI had significantly higher mortality (9.4% vs. 7.5%, $p<0.0001$) and longer median LOS (9 days vs. 4 days, $p<0.0001$).

We hypothesize that the increased risk for mortality seen among cancer patients is likely related to the overall underlying health status. Cancer is associated with higher mortality compared to the general population and CDI may simply exacerbate this association. Furthermore, in this dataset, cancer patients were older and had higher rates of other comorbidities. We were not able to verify cause of death; therefore, death could have been specifically related to the cancer, CDI, or something entirely else.

Importantly, cancer diagnosis was not associated with a longer hospital length of stay or increased risk for CDI recurrence. This is in contrast to our prior work, which found that median LOS for cancer patients with CDI was significantly longer than non-cancer patients (9 vs. 4 days; $p<0.0001$). These prior data were taken from U.S. community hospitals, exclusive of veterans. The older, generally sicker veteran population may help explain these differences. The higher rates of mortality among cancer patients may help explain the lack of association between cancer and CDI

recurrence – cancer patients may die before they have the chance to develop recurrence (i.e., survival bias).

Hematologic malignancies were especially related to increased risk for mortality. We believe that this is also related to underlying health status and general progression of cancer as described previously. Similar to cancer status overall, hematologic malignancies were not associated with longer LOS or higher risk for recurrence compared to solid tumors.

Specific Aim 3

Aim 3 of this dissertation was a comparative-effectiveness study comparing oral metronidazole to oral vancomycin on CDI health outcomes among cancer patients. Interestingly, we found no significance difference between groups in risk for 30-day mortality; however, risk for 60-day CDI recurrence and hospital LOS ≥14 days were significantly increased among patients treated with vancomycin.

To our knowledge, no other studies have compared clinical outcomes between metronidazole and oral vancomycin-treated patients, specifically in the cancer population. Metronidazole therapy, in general, has fallen out of favor due to a single clinical trial in non-cancer patients that demonstrated significantly higher rates of clinical cure with oral vancomycin.[72] A more recent randomized controlled trial found higher clinical cure among CDI cancer patients treated with fidaxomicin compared to vancomycin.[73] While our results are somewhat different than these prior studies, a recent study in the VHA found that metronidazole was not associated with increased mortality risk compared to vancomycin in younger (<65 years old) VA patients with mild CDI.[81] Our findings suggest that metronidazole may still be appropriate for veterans with CDI.

Although mortality was not significantly different between groups, vancomycin use was associated with significantly higher rates of CDI recurrence and longer hospital LOS. While we cannot determine the reason for this association in the current analysis, we suspect this is due to access issues in the outpatient setting. While metronidazole is available as an oral capsule and is dosed twice daily, oral vancomycin capsules are significantly more expensive and are dosed four times per day. Many patients were expected to locate a compounding pharmacy to access oral vancomycin compounded from the intravenous solution. This could considerably impact patient compliance, though

studies validating this association are lacking. In 2018, an oral vancomycin suspension was approved, which is less expensive than the capsules. This may aid in improved access in the outpatient setting in the future.

Study Strengths

This study has several strengths. First, we collected data on all patients with CDI managed at any VHA facility over a 12-year period. The VHA is the largest integrated health care system in the U.S. and is national in scope. This provided for a large sample size, which enabled more robust statistical analyses. These data supplement existing national database CDI studies that do not include information on federal facilities (e.g., CDC's National Hospital Discharge Surveys, AHRQ's Healthcare Cost and Utilization Project, AHRQ's Medical Expenditure Panel Surveys).

The VHA maintains a comprehensive computerized system that contains patient and provider demographics, inpatient and outpatient data, laboratory data, and pharmacy data. This enabled the study of many relevant variables and patient outcomes. We studied objective variables that are readily obtained in the normal course of a patient's clinical evaluation. We included variables that have been previously identified as risk factors for CDI and its outcomes. We also identified previously unknown CDI risk factors.

The VHA enabled us to collect data on outpatient CDI. Outpatients have rarely been studied previously due to lack of reporting and follow-up in the outpatient setting. The VHA system allowed us to capture outpatient information, thus filling a significant knowledge gap regarding the epidemiology of community-onset CDI.

CDI disproportionately affects older patients and those with underlying conditions; the VHA population is a major asset in that regard. Although men and elderly patients are over-represented in this population, as compared to community hospitals, this population is racially, ethnically, and medically diverse. Acute and chronic illness are common among VHA patients, thus our population is likely representative of CDI patients overall, with the exception of sex.

Study Limitations

This study has potential limitations. First, we utilized a retrospective study design that includes data collection from electronic medical records. This design has inherent limitations. Case-control and cohort studies might be subject to misclassification bias and confounding by unmeasured variables. Multivariable logistic regression techniques and internal validation were used in an attempt to account for confounders and limit any potential biases; however, these methods cannot fully account for all confounders and are not equivalent to a prospective, randomized study.

Specifically, we were unable to control for specific chemotherapy regimens in our analysis. Chemotherapy varies by regimen, different regimens for different cancer types. Different cancer severity may lead to different treatment intensity.

Cancer diagnoses don't account for late vs. early stage. A solid tumor could be a metastasis. Other cancer severity factors weren't included. Tried to use metastasis as a control for severity? Future study could focus on one cancer type, or compare those where the problem seemed really apparent.

The data were also collected from 2002 to 2014, which may not reflect current CDI epidemiology or treatment practices, especially with the release of the new CDI clinical practice guidelines in 2018. Drug selection preferences change over time. Perceived difference in treatment need due to severity of illness or overall health state may lead to "sicker" patients being treated with specific drug over another. General lag of real change after guideline publication. Cost also contributes largely. Future study could stratify by year.

The use of electronic medical records for data collection is also subject to limitations. Electronic medical data are created for the purpose of patient care, not for

research, and might contain errors. There might be variation in the extent of physician reporting of certain medical conditions; variability might lead to inaccuracy of the Charlson comorbidity score and other variables. Importantly, we relied on ICD-9-CM codes and CCS codes to identify CDI and other comorbidities. Although prior studies have demonstrated good sensitivity and specificity of CDI ICD-9-CM codes (71 to 78% and >99%, respectively) compared to microbiologic data,[82] administrative data might not fully capture every patient with CDI. Similarly, other comorbidities might not be fully captured using administrative codes and cannot be considered equivalent to medical chart reviews. Furthermore, fidaxomicin and other CDI therapies (FMT, rifaximin, nitazoxanide) use were low in this population; thus, we were not able to compare its effects on CDI clinical outcomes.

Finally, this study contained a predominately male VHA population; therefore, study findings might not be generalizable to non-VHA care settings.

Conclusions & Future Directions

CDI is an important public health problem in the Veterans Health Care System. In this nationally representative study of veterans, we found that cancer was an independent risk factor for CDI. Certain types of cancers were more strongly associated with CDI, including metastatic cancer and lymphatic/hematologic cancers. Next, cancer was an important risk factor for poor CDI health outcomes. Patients with cancer who develop CDI and more likely to experience 30-day all-cause mortality compared to those without cancer; however, cancer does not appear to strongly influence CDI recurrence or hospital LOS. Finally, CDI cancer patients treated with metronidazole or vancomycin had similar risk for 30-day mortality, but vancomycin was associated with a higher risk for recurrence and longer hospital stay.

CDI treatment and preventative initiatives should remain a national priority in the U.S. Newer therapies and clinical strategies are needed to reduce the risk of CDI and recurrences and improve the health outcomes of patients with CDI. Given that cancer patients are at higher risk for CDI compared to non-cancer patients, this group should be specifically targeted for preventative initiatives. Further studies are also needed to explore the optimal treatment strategies for patients with cancer who develop CDI.

GLOSSARY

Abbreviation	Definition
AIDS	Acquired immunodeficiency syndrome
CA-CDI	Community-associated *C. difficile* infection
CDI	*Clostridioides difficile* infection
CHF	Congestive heart failure
CI	Confidence interval
CO-HCFA-CDI	Community-onset, healthcare facility-associated CDI
COPD	Chronic obstructive pulmonary disease
CO-HCFA-CDI	Community-onset, healthcare facility-associated CDI
CRP	C-reactive protein
FDX	Fidaxomicin
FMT	Fecal microbiota transplantation
GAS	Gastric acid suppressant
GERD	Gastroesophageal reflux disease
HCFO-CDI	Healthcare facility-onset CDI
HIV	Human immunodeficiency virus
H2RA	Histamine-2 receptor agonist
HSCT	Hematopoietic stem cell transplant
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IDSA	Infectious Diseases Association of America
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICU	Intensive care unit
IV	Intravenous
LOS	Length of stay
OR	Odds ratio
PO	Per oral (route of administration)
PPI	Proton pump inhibitor
PR	Per rectum (route of administration)
SCFA	Short-chain fatty acid
SCr	Serum creatinine
SHEA	Society for Healthcare Epidemiology in America
US	United States
VHA	Veterans Health Administration
VINCI	Veterans Affairs Informatics and Computing Infrastructure
WBC	White blood cell

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